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TITLE: Fish Oil Supplementation and Fatty Acid Synthase Expression in the Prostate: A Randomized Controlled Trial

PRINCIPAL INVESTIGATOR: Jackilen Shannon, Ph.D.

CONTRACTING ORGANIZATION: Oregon Health and Science University
Portland OR 97239-0396

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14. ABSTRACT: One in seven men over the age of 60 will be diagnosed with prostate cancer. Elucidation of early cellular changes that may predict progression to prostate cancer and the identification of factors that may inhibit or reverse these cellular changes would be of great clinical significance. Alteration of the fatty acid synthase (FAS) pathway is an early cellular change that has recently come under investigation. Overexpression of the lipogenic enzyme FAS has been noted in several tumor and pre-cancerous tissue types, including prostatic intraepithelial neoplasia (PIN) and prostate cancer and has been suggested as an independent predictor of disease stage. Additionally, inhibition of FAS has been demonstrated to induce apoptosis and reduce cell proliferation in cancer cells. Fatty acid synthase expression in cancer and normal cells is regulated by the transcription factor sterol regulatory element binding protein 1c (SREBP-1). The up-regulation of SREBP-1 in tumor cells results in increased FAS expression and fatty acid synthesis. Research in normal cells has demonstrated that dietary supplementation with polyunsaturated fatty acids (PUFA), particularly omega-3 fatty acids, inhibits SREBP-1 activation, resulting in a decreased transcription of FAS.

15. SUBJECT TERMS
Prostate Cancer; Lipid Medtabolism, Clinical Trial; Omega-3 Fatty Acids

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INTRODUCTION

We are conducting a double-blind, placebo-controlled, randomized intervention study to evaluate the effects of Fish Oil (FO) supplementation on markers of lipid metabolism in prostate tissue samples. The primary endpoints of this trial are fatty acid synthase expression, caveolin-1 expression, changes in lipid raft fractions in the plasma membrane and cell proliferation (Ki-67 expression) in benign, pre-neoplastic and neoplastic prostate tissue. The secondary endpoints include measuring the expression of SREBP-1, a transcription factor for fatty acid synthase, cell death (apoptotic fraction using TUNEL), red blood cell (RBC) fatty acid concentration and change in PSA. Subjects are men from the Portland VA Medical Center (PVAMC), the Oregon Health and Science University (OHSU) and Kaiser Permanente Northwest (KPNW) urology clinics who are scheduled for a repeat biopsy. These men will have had an initial negative biopsy yet are still considered at high risk due to continued elevated prostatic specific antigen (PSA >4μg/dl), are positive for PIN, have suspicious findings by DRE or TRUS, or other clinical finding. Approximately 80 men total will be recruited and randomized to receive three months of either fish oil capsules (treatment 1) or olive oil (placebo) capsules (treatment 2). Potential confounding variables are assessed through completion of a comprehensive diet history questionnaire and risk factor questionnaire, assessment of pre and post-treatment PSA and surveillance of medication and supplement use. Compliance will be assessed using pill count and evaluation of RBC fatty acid concentrations. While this study population is limited to men at high risk of disease, the results may be more broadly generalizable to any man considered at risk of prostate cancer due to standard clinical indicators such as a PSA >4μg/ml.

FISH OIL TRIAL RECRUITMENT: SEPTEMBER 2006–MARCH 2009

Fish Oil Participant Status	
Total subjects referred: 167	**N (% of all eligible)**
Refusal for any reason:	**81**
Ineligible	**21**
Total subjects enrolled : Completed study: Active: Withdrawn:	**61** **49 (29%)** **8 (5%)** **4 (2%)**
Identified potential subjects awaiting eligibility determination	**4**
Total subjects enrolled through Fish Oil only trial	30
Total subjects enrolled through Fish Oil and Green Tea	31

BODY

Specific Aims: The aims as presented in the last annual report have not changed.

Studies and Results: During this year's budget period, we developed a revised protocol that streamlined our eligibility criteria and added an extra layer of MD oversight prior to randomization. Because of our delayed recruitment, it has been imperative to create new, more pro-active and aggressive recruitment methods with our collaborating clinicians. Over the past year, Ms. Courtney Maxcy completed her training with Ms. Alysia Cox and is now solely responsible for this trial. Ms. Maxcy has initiated new recruitment activities, and now visits one of the two Kaiser clinics every week to maintain

relationships with the clinicians, checks with the OHSU clinic regularly and is working closely with the PVAMC clinician and his nurse to monitor for potential subjects and increase recruitment. Despite the fact that Dr. Mitchell Sokoloff (collaborator) left OHSU last year, Dr. Christopher Amling has recently replaced him. We have met with Dr. Amling to explain this study and request his prostate biopsy referrals; he is amenable to the collaboration and very interested in being involved in the research. This diligent work with the clinicians to enhance recruitment has been successful and we are now seeing a dramatic increase in recruitment. Since February 2008, we have successfully enrolled 25 men into the trial. Four additional men have been referred and will be contacted in the next week to confirm interest and eligibility. We are now averaging recruitment of approximately 5 to 7 new subjects per month, and believe that our numerous efforts in revitalizing this trial are now paying off with enhanced recruitment. These activities are directly related to Tasks 1 and 2 in our Scope of Work (Appendix 1).

In addition, over the past year, we have continued work to optimize our laboratory procedures for estimating lipid raft and total cholesterol content within the prostate biopsy specimens. Our original lipid raft protocol was developed using surgical prostate samples. However, when we attempted to use this protocol with two different needle stick biopsy samples we were not able to obtain detectable raft fractions. As a result, we assessed the possibility of using the needle stick biopsy samples for total cholesterol analysis using the Amplex Red Cholesterol Kit. Biopsy samples were homogenized directly in the assay buffer and a sample removed for protein analysis. We removed different amounts of total protein and found that 10 to 20 µg of total protein provided a reliable and reproducible cholesterol determination. In 2 different biopsy samples we found a range of 5 to 20 ng cholesterol/ µg of protein. In discussions with Dr. Koop, Dr. Thuillier and Dr. Shannon's colleague at Oregon State University (Dr. Donald Jump), it was determined that a more meaningful use of these tissue specimens would be to determine total fatty acid content in the post-intervention tissue. These analyses, offered at no cost by Dr. Jump, an expert in the field of fatty acid metabolism, will provide us with the only data available to date on the effectiveness of fish oil supplements in changing prostate tissue specific fatty acid levels. This information will be key to the successful development of other protocols predicated on the assumption that circulating levels of fatty acids reflect changes in prostate tissue levels of these bioactive compounds. This information will also allow us to begin exploration of how fatty acid metabolism may be altered within the cancerous tissue as compared to non-cancerous tissue. We have begun the creation of a materials transfer agreement with Dr. Jump and upon completion will transfer samples to his laboratory for analyses.

HUMAN SUBJECTS REVIEW: Oversight for our protocol was transferred to USAMRMC HRPO on 1 September 2006; all minor modifications were reported to HRPO at the time of Continuing Review for all three sites. We utilize the HRPO Continuing Review Checklist annually and write corresponding explanation memos for these submissions to HRPO. Summary of local human subjects review follows:

For log number A-12538.a (PVAMC), the DOD HRPO received PVAMC's last two Continuing Reviews (PVAMC approvals 5/2/2007 and 3/14/2008) in June 2007 and April 2008. For log number A-12538.b (OHSU), the DOD HRPO received OHSU's continuing review submission (OHSU approval: 2/7/2008) in April 2008. For log number A-12538.c (KPNW), the DOD HRPO received KPNW'S continuing review submission (KPNW approval: 7/16/2008) in August 2008. The trial underwent an annual Data Safety Monitoring Committee Audit by the OHSU Knight Cancer Institute and was found to be fully compliant. See attached Audit report (Appendix 2).

STUDY COORDINATION: Ms. Courtney Maxcy has taken on the role of primary staff responsible for patient contact and recruitment procedures as well as on-going contact with collaborating clinicians. As described previously, Ms. Maxcy has maintained the pro-active and aggressive recruitment methods with our collaborating clinicians since taking over study responsibility. She visits the two Kaiser clinics regularly to maintain relationships with the Kaiser clinicians. We have made contact with the new urologist at OHSU to discuss the study and anticipate he will begin recruitment in mid-March 2009. Ms. Maxcy continues to work closely with the PVAMC clinician and his nurse to increase recruitment. Ms. Farris retains primary responsibility for human subjects' paper work, continuing review documents and maintains annual contact with Johanna Kidwell (CDMRC). All of Dr. Shannon's team – numbering four – are cross-trained and can assist with subject visits, follow-up and biopsy core processing, as necessary.

PROGRESS TO DATE: We have begun to obtain pre and post-intervention prostate biopsy tissue from each hospital's pathology department for data analysis. We are working closely with staff at the Kaiser Permanente NW pathology archive to develop a protocol for tissue ascertainment and analyses. Dr. Christopher Corless, director of the OHSU pathology core, has agreed to conduct all secondary reading of H&E slides for re-cut and his laboratory is responsible for all immunohistochemical staining. As stated last year, immunohistochemistry for fatty acid synthase (FAS) and sterol regulatory element binding protein (SREBP-1) in the biopsy samples will occur in our final year of funding to allow for batching of the work and to ensure that the technicians are unaware of subject status when reviewing the samples.

KEY RESEARCH ACCOMPLISHMENTS: Our key accomplishments over the past year have been the development of a successful and consistent method for study recruitment. We have continued to develop the necessary protocols for laboratory analyses. As this is a double-blind clinical trial we have not conducted any preliminary analyses to date.

REPORTABLE OUTCOMES: None to date

CONCLUSIONS: The primary outcome of the past year was the sustained and aggressive effort toward subject recruitment. Ms. Maxcy has very successfully enhanced recruitment to this study over the course of a year. We, therefore, anticipate reaching our original recruitment goal of 80 men within the next few months. As of March 11th, we received a no-cost extension from Ms. Shannyn Scassero for one year to allow us to complete our planned laboratory and statistical analyses. These analyses will include erythrocyte fatty acid analyses and immunohistochemical analysis of pre and post intervention biopsy specimens, as well as fatty acid analyses in frozen biopsy specimens.

C. Revised Statement of Work, version 4

Fish Oil Supplementation and Fatty Acid Synthase Expression in the Prostate: A Randomized Controlled Trial

Task 1. Finalize clinical protocol and training: Months 1-6 **(Completed)**

a. Develop tracking system for recording patient recruitment, contact and consent information.
b. Obtain IRB approval from Portland VA Medical Center (PVAMC), Oregon Health and Sciences University (OHSU) and Kaiser Permanente Northwest (KPNW).
c. Finalize encapsulation procedure and obtain treatment and placebo capsules.
d. Finalize and review clinical protocol with GCRC nursing staff.
e. Review and optimize blood processing procedures with laboratory staff.
f. Review procedures for patient contact and recruitment with (PVAMC) Mark Garzotto, MD, Laura Peters, RN and study coordinator, Amy Palma.
g. Modify tracking system, protocol, and consent form to allow for the collection of an additional prostate biopsy core to be cryopreserved.

Expected Product: Tracking system, IRB approval, IRB approval of amendment.

Task 2. Subject recruitment and data collection Months 1 – 9 (Complete by 5/2009)

a. With the addition of two study sites (IRB and DOD approved); review procedures for patient contact and recruitment with (OHSU) Mitchell Sokoloff, MD and Mark Johnson, RN; (KPNW) Stephen Lieberman, MD.
b. Patient Eligibility and Recruitment:

1. **Pre-Recruitment Screening**

- Clinician recommends repeat biopsy of the prostate

2. **Inclusion**

- Age 21 years or older
- Signed informed consent form

3. **Exclusion**

- Definitive prostate cancer on initial biopsy
- Significant active medical illness that in the opinion of the clinician would preclude protocol treatment.
- History of ventricular tachycardia or ventricular fibrillation
- Patient reported use of fish oil (at greater than 1 gram per day) or green tea supplement within 30 days before Day 1 of study treatment
- Use of warfarin or need for therapeutic anticoagulation at time of biopsy or at anytime during the course of the trial.
- Subject reported allergy or sensitivity to fish oil, olive oil or green tea
- Subject reported history of hemophilia, van Willebrands disease or other bleeding disorder, except when the subject is evaluated by a hematologist who determines that fish oil supplementation is not contraindicated.
- Total bilirubin greater than institutional upper limit of normal
- VA subjects may not be a part of another 'flagged' high risk study as noted, in red, on the cover sheet of subjects' VISTA/CPRS electronic medical record.

c. Initial telephone contact and schedule appointment.
d. 1st visit – at the OHSU GCRC-- Informed consent process; Initial study procedures:
   i. Outpatient specimen collection form (including height, weight and blood pressure) and inquire about recent history of concerns that would preclude phlebotomy
   ii. Blood draw for baseline red blood cell fatty acid assessment (10mL)
   iii. Blood draw for analyses of serum osteocalcin (10mL)
   iv. Blood draw for baseline total bilirubin test (5mL)

v. Urine collection for measures of bone turnover
vi. Study Questionnaires (Adverse Event and Diet History Questionnaire (DHQ) and Risk Factor Questionnaire)
vii. Randomization

e. Eligibility confirmation -Four week supply of placebo or treatment capsules distributed.
f. 2nd visit – at the OHSU GCRC (for subjects residing outside the Portland area, this visit may be replaced by a telephone contact and mailed supplements)
- Four week supply of placebo or treatment capsules distributed.
- Complete side-effects and adverse events reporting form.

g. 3rd visit – at the OHSU GCRC (for subjects residing outside the Portland area, this visit may be replaced by a telephone contact and mailed supplements)
- Four week supply of placebo or treatment capsules distributed.
- Complete side-effects and adverse events reporting form.

h. 5th visit – at PVAMC clinic area E or OHSU or KPNW Urology clinics
- Return unused capsules.
- Obtain 20 ml blood specimen
- Repeat biopsy conducted per standard clinical procedure (this is not a study linked event)
- Obtain two additional biopsy cores for cryopreservation and analyses of lipid raft fractions.

In men with known prostate cancer this core will be taken, if possible, from the quadrant farthest from the known tumor. Fresh tissue collected at surgery by study RA and delivered immediately to the OHSU Pharmacokinetics Core for cryopreservation.

Expected Product: Questionnaire, blood specimen and biopsy (frozen and paraffin embedded) data for **80** patients (original number for which funding was received).

Task 3. Preparation for Immunohistochemistry (IHC) / Data Entry. Months 13-24 (**Complete)**

a. Optimize IHC for fatty acid synthase (FAS) and sterol regulatory element binding protein (SREBP-1)
b. Optimize protocol for lipid raft extraction from tissue specimens (using stored non-study tissue).
c. Develop database for tracking specimen receipt and analysis
d. Begin data entry of questionnaire forms and event reporting forms

Expected Product: High functioning antibodies and procedures for FAS and SREBP-1 IHC, final procedures for lipid extraction and raft associated protein analyses, laboratory database, complete questionnaire data entry.

Task 4. Laboratory / Dietary Analyses. Months 6-11

a. Blood specimens shipped to Seattle for red blood cell fatty acid analyses.
b. Initial and repeat biopsy specimens obtained from PVAMC / OHSU / KPNW pathology.
c. Perform IHC for FAS ~~and SREBP-1~~ on pre and post intervention tissue specimens.
d. Perform IHC for Ki-67 and TUNEL assay on post-intervention tissue specimens.
e. **Perform full fatty acid panel analyses on post-intervention frozen tissue using HPLC**.
f. Run nutrient analysis program on diet history questionnaire data.
g. Data cleaning.

Expected Product: Complete data on FAS ~~and SREBP-1~~ expression in **160** tissue specimens from **80** patients. Complete data on Ki-67 expression and TUNEL for **80** tissue specimens from **80** patients. **Complete data on distribution and type of fatty acids in the frozen biopsy specimens.** Red blood cell fatty acid concentrations from **160** blood specimens from **80** patients. Nutrient intake data from 80 patients.

Task 5. Final Analyses and Report Writing Months 10-12

a. Final analysis of data from questionnaires, blood specimens and tissue specimens will be performed
b. Prepare final report and initial manuscripts.

Expected Product: Completed and submitted final report a minimum of 1 submitted manuscript.

October 14th, 2008

Jackie Shannon, PhD
CB669
Oregon Health and Science University/Veterans Affairs Medical Center

RE: *CPC-04131-LX "Fish Oil Supplementation and Fatty Acid Synthase Expression in the Prostate: A Randomized Controlled Trial* (IRB # 1117)

Dear Dr. Shannon:

A quality assurance audit by the Data and Safety Monitoring Committee (DSMC) was conducted on October 13th, 2008. Bashi Ratterree, Kristin Hackney, and Lora Wilson conducted the audit. The study coordinator, Courtney Maxcy, assisted with the audit. The accrual goal for this study is 160 and to date 50 subjects have been enrolled at all sites. Records were audited for 2 subjects: **KW enrolled 06/26/2008 and DL enrolled 01/31/2008.**

The regulatory binders were found to be in good order; however, OCI has no record of any of the VA or Kaiser regulatory submissions. Nor, do we have record of any of those IRB approvals for those sites. Please make copies of all VA and Kaiser regulatory submissions and their subsequent approvals and submit to us. Please remember that all VA submission materials need to have an OCI approval signature prior to submission to the VA IRB. This can be done by submitting them to Kristin Hackney. Staff at OCI will ensure submission to the VA IRB after OCI review.

Copies of the approvals from VA and Kaiser IRBs must also be sent via interoffice mail to OCI. In addition, we would like to ask that audit letters be separated into a separate QA section of the binder.

Please inform the committee whether Kaiser Permanente is conducting audits of subject records. If so, please forward the results letters to the DSMC.

KW:

- Per protocol, the clinician screening questions should occur post-informed consent. For this subject, the clinician conducted the screening prior to and after

consent. It is recommended that because the timing of the screening questions is explicit in the protocol it must be followed.

DL:

- Eligibility criteria excludes subjects with positive findings on initial biopsy. The chart did not contain copies of all prior biopsies. The study coordinator stated that "initial biopsy" refers to the screening biopsy. It was recommended that all prior biopsies be included in the chart for source documentation. Please explain what is meant by "initial biopsy" and why prior biopsies were not included in the chart.
- Patient medication diary is missing. There are no notes in the chart stating that compliance with study regimen was confirmed. This was discussed with the coordinator who states the diary was not retrieved from the patient. Please explain how compliance to study regimen will be confirmed for this and other subjects.
- Pharmacy orders had a late entry by coordinator "AC". The late entry is dated with an incorrect year. Courtney Maxcy stated she will correct the date and initial.
- A note to file was written regarding an event on 4/8/2008. There is no date noting when the note to file was created. A write-over correction was also made on this document rather than single line with initial. This was discussed with the coordinator and corrected.

This audit has been rated Acceptable, Needs Follow Up. Please respond within 30 days. We thank Courtney Maxcy for her assistance during this audit. If you have any questions please do not hesitate contact me at 4-1028.

Sincerely,

Bashi Ratterree, RN, BSN, CCRP
DSMC Co-Chair/Quality Assurance Auditor
OHSU Cancer Institute

CC: Courtney Maxcy, Jackie Shannon

October 15, 2008

Bashi Ratterree, RN, BSN, CCRP
DSMC Co-chair
OHSU Cancer Institute

RE: CPC-04131-LX (VA/OHSU IRB # 04-0303): *Fish Oil Supplementation and Fatty Acid Synthase Expression in the Prostate: A Randomized Controlled Trial*

Thank you for your ongoing review of the above-mentioned trial. This letter is in response to OCI Data and Safety Monitoring Committee (DSMC) memo dated 10/14/08. Please accept our responses to the quality assurance audit by the DSMC conducted on 10/13/08. Bashi Ratterree, Kristin Hackney, and Lora Wilson conducted the audit. Records were audited for 2 subjects: **KW enrolled 06/26/2008 and DL enrolled 01/31/2008.**

OCI has no record of any of the VA or Kaiser regulatory submissions. Nor, do we have record of any of those IRB approvals for those sites. Please make copies of all VA and Kaiser regulatory submissions and their subsequent approvals and submit to us.

We have addressed this issue by copying our VA and Kaiser regulatory submissions and presenting them to Kristin Hackney in binder form. Our team has discussed this issue and is developing a strategy in order to ensure OCI receives all VA and Kaiser regulatory documents in a timely fashion (in the case of the VA, prior to submission to the VA).

In addition, we would like to ask that audit letters be separated into a separate QA section of the binder.

There is now a separate audit section in our regulatory binders.

KW:

Per protocol, the clinician screening questions should occur post-informed consent. For this subject, the clinician conducted the screening prior to and after consent. It is recommended that because the timing of the screening questions is explicit in the protocol it must be followed.

We apologize for any confusion in our protocol. As noted in Section 3 A of our protocol, Subject Identification and Recruitment, "… If they have <u>met inclusion criteria according to a clinician</u> and have expressed interest, a consent form will be given to the potential subject for review prior to Visit 1. If there is continued interest, a Visit 1 appointment will be set-up." This is then followed by Section 3.B in which informed consent is provided and finally, "After the informed consent process and Visit 1 study procedures have taken place, the name and phone number of consented subjects will be given to the <u>clinician to complete the final eligibility screen</u>."

Thus the screening interview and questions completed prior to consent are solely to determine interest and whether the subject meets inclusion criteria. This is not a source document, but rather a contact sheet that allows the clinician to inform the coordinator of interested subjects and pre-screen such that we are not burdening men who clearly do not meet inclusion criteria with a trip to OHSU and a baseline visit. This approach is somewhat unique but was developed and agreed upon through discussion with OCI DSMC auditors, study clinicians (Drs Garzotto and Beer) and Dr. Shannon following the 2007 OCI audit.
If it would be useful, we can further clarify this order of events in our protocol and change the title of our current form from CONTACT SHEET FOR INTERESTED SUBJECTS to more clearly state pre-screen inclusion checklist.
DL:
Eligibility criteria excludes subjects with positive findings on initial biopsy. The chart did not contain copies of all prior biopsies. The study coordinator stated that "initial biopsy" refers to the screening biopsy. It was recommended that all prior biopsies be included in the chart for source documentation. Please explain what is meant by "initial biopsy" and why prior biopsies were not included in the chart.
For this trial, initial biopsy is defined as the pre-intervention biopsy, or the first biopsy of the study. While subjects may have undergone any number of prior biopsies, our exclusion criteria is based solely on the biopsy after which the clinician introduced the study to the subject. Because subject eligibility is not altered by findings from any other prior biopsies and no study activities or analyses make use of these prior biopsies, we feel it would be inappropriate to maintain this additional PHI in our study charts. We have altered our operations manual to note that if pathology data is provided for any other biopsies prior to our "initial" study biopsy this information is to be destroyed or "x"ed out using a wax pencil.
Patient medication diary is missing. There are no notes in the chart stating that compliance with study regimen was confirmed. This was discussed with the coordinator who states the diary was not retrieved from the patient. Please explain how compliance to study regimen will be confirmed for this and other subjects.
In the future, study coordinators will ask study subjects who do not return a supplement diary to verbally confirm how many pills were missed (and when) in order to determine subject compliance. Subject will be given a postage-paid envelope asked to mail the diary to staff, and during the visit 5 follow up phone call, coordinator will remind subject. The study coordinator will include this information in the progress note. Further confirmation of subject compliance is obtained through record of supplements returned to the research pharmacy each month and through analysis of erythrocyte fatty acid levels at study completion.
Pharmacy orders had a late entry by coordinator "AC". The late entry is dated with an incorrect year. Courtney Maxcy stated she will correct the date and initial.
Alysia Cox and Courtney Maxcy have resolved this issue.
A note to file was written regarding an event on 4/8/2008. There is no date noting when the note to file was created. A write-over correction was also made on this

document rather than single line with initial. This was discussed with the coordinator and corrected.
Alysia Cox and Courtney Maxcy have resolved this issue.

Thank you for the time and patience you have taken in reviewing our trial. My goal and the goal of my research staff is to ensure that our trial meets the highest standards for both scientific and regulatory review. Please contact us with any further questions.

Sincerely,

Jackilen Shannon, PhD, RD
Scientist / Assistant Professor
CROET / Public Health & Preventive Medicine
3181 SW Sam Jackson Park Road
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Portland, OR 97239
503-494-4993 (Mon – Wed)
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November 4, 2008

Jackie Shannon, PhD
CB669
Oregon Health and Science University/Veterans Affairs Medical Center

RE: *CPC-04131-LX "Fish Oil Supplementation and Fatty Acid Synthase Expression in the Prostate: A Randomized Controlled Trial* (IRB # 1117)

Dear Dr. Shannon:

Thank you for your response dated October 15, 2008, regarding the findings of the quality assurance audit by the Data and Safety Monitoring Committee (DSMC) that was conducted on October 13, 2008.

This letter is to inform you that the audit is now complete. Suggestions made at the time of the audit have been implemented and all issues have been reconciled.

Please remember to send a copy of audit letters to IRB at continuing review. We will continue to audit this study per the DSMP.

We thank Courtney Maxcy for her assistance during this audit. If you have any questions please do not hesitate contact me at 4-1028.

Sincerely,

Bashi Ratterree, RN, BSN, CCRP
DSMC Co-Chair/Quality Assurance Auditor
OHSU Cancer Institute

CC: Courtney Maxcy